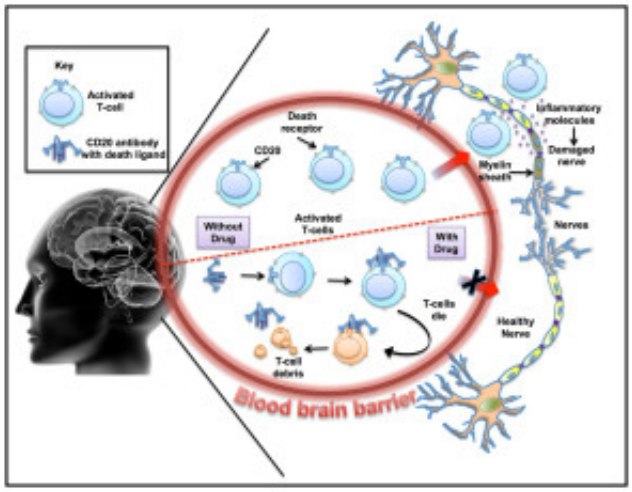
Selectively killing T-cells in multiple sclerosis: A brainy approach

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that often afflicts young people. The nerve fibres in the brain, which transmit the electrical impulses that control many of the common functions of the body such as walking, balance and sight are damaged. An insulating protective coat protein called myelin protects these nerves. Unfortunately, in MS, white blood cells are signalled by as yet unknown means to move from blood into the brain and target the myelin for destruction. This leaves the nerve fibres susceptible to damage by particular blood cells called T-cells. These T-cells signal to other brain cells to cause further damage to these nerve cells. Thus, MS is an autoimmune disease where your T-cells that normally fight infections destroy their own tissues. There are no cures currently for multiple sclerosis. We can suppress the autoimmune responses that develop in MS patients.



A strategy for dealing with MS is to suppress the autoimmunity. We know how infections activate our immune systems and which blood cells eliminate microorganisms. When we recover from infections, our body naturally uses specific blood proteins, neutralising antibodies produced by B-cells and specialist cells to dampen down our immune response. Ironically, sometimes these ‘friendly’ immune cells e.g. B-cells, may encourage autoimmune T-cells to develop. Fortunately we have a number of drugs that can prevent these T-cells crossing from the blood into the brain, or prevent their deleterious activation. Sometimes a drug that is effective for one autoimmune disease is tested on patients with a different autoimmune disease. This approach may sound somewhat serendipitous in nature but can be quite effective. In the case of MS, drugs used to eliminate antibody-producing B-cells (not generally considered the main culprits in MS) do often alleviate the symptoms of MS, allowing the patient to go into remission. One such drug is anti-CD20 antibody, a manufactured antibody that binds to an innocuous protein present on the surface of most peripheral blood B-cells called CD20. Once bound, antibodies against CD20, flags these cells for eventual destruction by our immune system.

Although MS pathology is thought to be caused by autoreactive T-cells crossing into the brain, one rationale for using a drug designed to kill B-cells is that the B-cells might prime the T-cells to become inflammatory, before they move to the brain and cause damage. Our collaborative studies with colleagues from the University of Exeter and Groningen have identified a small but significant number of T-cells in the blood and brains of MS patients that also have CD20 on their cell surface. We have found these CD20+ T-cells in other autoimmune disease and cancer patients recently. These CD20+ T-cells possess an array of pro-inflammatory molecules that can potentially cause damage once they enter the brain. We tested commercially available anti-CD20 drugs to kill these T-cells, but they were not very effective, because T-cells have much less of the CD20 molecule on their cell surface for the drug to bind to compared to B-cells. So we engineered a ‘super’ antibody against CD20 that binds to the CD20 molecule on T-cells and then uses another protein attached to the antibody to directly kill the activated T-cells and not B-cells.

This drug worked much better as it does not wait on the body’s immune system to kill the T-cells, but can do so directly. It is quite specific as it targets the T-cells we believe move to the brain and cause direct damage. Drugs designed in this manner can potentially be used to kill CD20+ T-cells without the need to kill other important immune cells unnecessarily.

Publication

CD20+inflammatory T-cells are present in blood and brain of multiple sclerosis patients and can be selectively targeted for apoptotic elimination.
Holley JE, Bremer E, Kendall AC, deBruyn M, Helfrich W, Tarr JM, Newcombe J, Gutowski NJ, Eggleton P
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